

*G 4*  
*Control*  
the at least one sugar chain is covalently bonded through the peptide sequence to which the at least one sugar chain is added, thereby increasing the residual activity of the heparin-binding protein, said at least one sugar chain selected from the group consisting of a sulfated polysaccharide, a glycosaminoglycan, an O-linked sugar chain combined with a sulfated polysaccharide or a glycosaminoglycan, an N-linked sugar chain combined with a sulfated polysaccharide or a glycosaminoglycan, and combinations thereof.

*G 5*  
23. (Amended) A heparin-binding protein which comprises a heparin-binding protein modified with covalently bonded sugar chains, the sugar chain being selected from the group consisting of a sulfated polysaccharide, a glycosaminoglycan, an O-linked sugar chain combined with a sulfated polysaccharide or a glycosaminoglycan, an N-linked sugar chain combined with a sulfated polysaccharide or a glycosaminoglycan and combinations thereof, wherein the activity of the heparin-binding protein is greater than the activity of the unmodified protein.

#### REMARKS

This Amendment is submitted in response to the Office Action dated November 13, 2002. Reconsideration and withdrawal of the rejection of this application in view of the amendments made herein and the remarks set forth below are respectfully requested.

Claims 1, 3-6, 14, 17-21, 23-28 are pending in this application. In this Response, claim 16 has been canceled without prejudice and claim 1 has been amended. No new matter has been added.

Applicant first notes with appreciation that the Examiner has withdrawn his rejections under 35 U.S.C. §112 first paragraph for new matter in the recitation "one or more" or "plurality of" in conjunction with "sugar chains" and in the recitations of "activity" and of "heparin binding protein" comprising a "peptide" in claim 20. Applicants agree that the peptides added to the heparin binding protein would contain multiple sites at which sugar chains would be added and that, if the sugar chains were to be chemically coupled, then there would inherently be multiple amino and/or hydroxyl groups in the heparin binding protein available for such coupling.

In the November 13, 2002 Office Action, the Examiner newly rejected claims 1, 3-6, 14, 16-21, 23-28 under 35 U.S.C. §112, second paragraph, for failing to particularly point out and distinctly claim the subject matter of the invention. In particular, the Examiner stated that

- (1) in claim 1, line 2, "being" is extraneous;
- (2) in claims 1, 6, 16, 19-20 and 23, "the residual activity" is not clear because (i) it is not clear what kind of "activity" is intended (heparin binding activity or other protein activity, such as growth promoting activity); (ii) it is not clear what the "residual activity" is compared to (glycosilated protein?); and (iii) it is not clear if there is some process or treatment that the protein is subjected to (such as a destabilizing process) to determining how much "residual activity" remains;
- (3) in independent claims 1, 16 and 18-20, the third and fourth members of the Markush grouping of sugar chain are not clearly recited, since it is not clear how the "O-linked (or N-linked) sugar chain combined with a sulfated polysaccharide or glycosaminoglycan" is so combined, and the Examiner cannot find a description of either in the original disclosure;
- (4) in claims 4, 16 and 18-20, "through a peptide" or "containing a peptide sequence" are not clear, since it is not clear how the peptide is structurally related to the heparin binding protein.
- (5) in claim 6, "near one of the ends" is a relative term that is not defined in the claim or specification, and it is also not clear if this addition must be at a residue within a heparin binding protein or can be at a residue of a peptide fused thereto;
- (6) in claims 5 and 17, part (b), "consists of" is closed language, whereas "addition" is open language;
- (7) in claim 17, part (b), line 4, "can be" is unclear and indefinite because the sugar chain may or may not be present; and
- (8) in claims 18, 20 and 23, the feature that is "improved" is not identified.

The Examiner also stated that, should claim 4 be found allowable, claim 16 will be objected to under 37 CFR 1.75 as being a substantial duplicate of claim 4, since claim 16 appears to have been written with all of the limitations of claim 1 and its dependent claim 4.

The Examiner further rejected claims 1, 3-6, 14-20 and 23 under 35 U.S.C. §112, first paragraph, for containing subject matter that was not described in the specification in a way that reasonably conveys to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, Examiner states that the third and fourth members of the Markush group of sugar chain in each of the independent claims contain new matter by reciting "combined with a sulfated polysaccharide or glycosaminoglycan". The Examiner further states that claim 23 also contains new matter by reciting "wherein the activity of the heparin binding protein is greater than the activity of the unmodified protein."

In response, Applicants have amended claim 1 to delete the extraneous word "being" line 2, have canceled claim 16, have amended claim 17 to change the words "can be" to "is", have amended claims 18, 20 and 23 to delete the word "improved", have amended claims 1, 16 and 18-20 to add a comma after the fourth Markush grouping element to separate the fourth and fifth Markush elements. It is believed that these amended claims obviate the rejections of these claims under 35 U.S.C. §§ 112, second paragraph, as set forth by the Examiner, and Applicants request that these rejections be withdrawn.

With respect to the rejection of claims 5 and 17, part (b), because "consists of" is closed language, whereas "addition" is open language, Applicants traverse this rejection. The term "consists of" is closed language and is proper usage when defining an acceptable form of alternative expression, commonly referred to as a Markush group. See, Manual of Patent Examining Procedure, § 2173.05(h). The word "addition", however, is used in claims 5 and 17 to define one of the elements within the Markush grouping. In this case, the element is "a protein which consists of the amino acid sequence of SEQ ID NO: 1, 3, 5, 17, 19, 21, 23, 25, 27 or 29 having a deletion, substitution, addition or modification of at least one amino acid, ...." This term "addition", whether or not objectionable for other reasons, describes only this element (b) in the Markush group and not the Markush group as a whole, which remains defined as the group encompassed by the term "consisting of". Accordingly, the term "addition" does not serve to expand the Markush group so as to render it indefinite, and Applicants request that this rejection be withdrawn.

With respect to the rejection of independent claims 1, 16 and 19-20 for the improper recitation of the third and fourth elements of the Markush grouping, Applicants respectfully traverse the Examiner's rejection. Applicants refer the Examiner to the portions of the specification at page 4, line 16 - page 5, line 3 and at page 7, line 28 – page 8, line 12 for specific disclosure of the linking of a sulfated polysaccharide or a glycosaminoglycan with either an O-linked sugar chain or an N-linked sugar chain. Accordingly, in view of the recited combinations that are present in the specification, Applicants submit that the Markush groupings are proper and find support within the specification, and Applicants request that the Examiner withdraw his rejection.

The Examiner also rejected all of claims 1, 3-6, 14, 16-21 and 23-28 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,486,599 (hereinafter "Saunders"). The Examiner alleges that the Saunders, et al. reference teaches all the limitations of these claims.

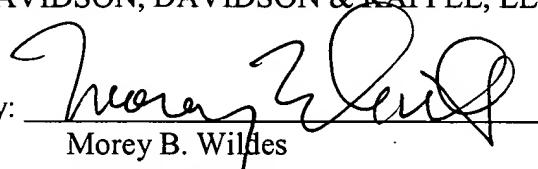
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In response to the rejection of claims 1, 3-6, 14, 16-21 and 23-28 under 35 U.S.C. § 102(b) as being anticipated by the Saunders reference, Applicants respectfully submit that Saunders does not enable the disclosures therein, instead providing merely speculative assertions relating to various combinations of molecules. Applicants remind the Examiner that, according to the Court of Appeals for the Federal Circuit, a "claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." See *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1334 (Fed. Cir. 2003). In this case, the language in the Saunders reference used by the Examiner to reject the claims under § 102(b) is entirely prophetic and does not provide any guidance to enable one skilled in the art to reduce to practice the invention as described therein. The Saunders reference does not itself enable the disclosures therein and thus cannot be used to anticipate the present claims. Accordingly, Applicants respectfully request that the rejection of anticipation based upon the Saunders reference be withdrawn.

In view of the amendments and remarks set forth herewith, Applicants believe that all claims are now in condition for allowance. In the event that the Examiner determines that the application is not in condition for allowance, Applicants respectfully request the Examiner to contact the undersigned for a telephone interview before another Office Action is issued in the application.

A favorable action on the merits is earnestly solicited.

Respectfully Submitted,  
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**VERSION OF AMENDMENTS  
WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE CLAIMS**

1. (Three Times Amended) A heparin-binding protein comprising at least one covalently bonded sugar chain, wherein the at least one sugar chain is [being] selected from the group consisting of a sulfated polysaccharide, a glycosaminoglycan, an O-linked sugar chain combined with a sulfated polysaccharide or a glycosaminoglycan, an N-linked sugar chain combined with a sulfated polysaccharide or a glycosaminoglycan, and combinations thereof, wherein the residual activity of the heparin-binding protein is increased by adding the at least one covalently bonded sugar chain.

16. (Thrice Amended) A heparin-binding protein comprising at least one covalently bonded sugar chain, wherein the at least one sugar chain is selected from the group consisting of a sulfated polysaccharide, a glycosaminoglycan, an O-linked sugar chain combined with a sulfated polysaccharide or a glycosaminoglycan, an N-linked sugar chain combined with a sulfated polysaccharide or a glycosaminoglycan, and combinations thereof, wherein the at least one sugar chain is covalently bonded through a peptide to which the sugar chain is added, thereby increasing the residual activity of the heparin-binding protein by adding the at least one covalently bonded sugar chain.

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claim 16*

17. (Amended) The heparin binding protein of claim 16, wherein the heparin-binding protein comprising the covalently bonded sugar chain comprises:

- (a) a protein consisting of the amino acid sequence of SEQ ID NO: 1, 3, 5, 17, 19, 21, 23, 25, 27 or 29; or
- (b) a protein which consists of the amino acid sequence of SEQ ID NO: 1, 3, 5, 17, 19, 21, 23, 25, 27 or 29 having a deletion, substitution, addition or modification of at least one amino acid, wherein the heparin-binding protein has FGF activity and the sugar chain [can be] is added thereto.

18. (Twice Amended) [An improved] A heparin-binding protein which comprises a heparin-binding protein functionalized by covalently bonding thereto at least one sugar chain, wherein the at least one sugar chain is covalently bonded through a peptide to which the sugar chain is added thereby increasing the residual activity of the heparin-binding protein, said at least one sugar chain selected from the group consisting of a sulfated polysaccharide, a glycosaminoglycan, an O-linked sugar chain combined with a sulfated polysaccharide or a glycosaminoglycan, an N-linked sugar chain combined with a sulfated polysaccharide or a glycosaminoglycan, and combinations thereof.

19. (Thrice Amended) A heparin-binding protein comprising a plurality of covalently bonded sugar chains, wherein the sugar chains are selected from the group consisting of a sulfated polysaccharide, a glycosaminoglycan, an O-linked sugar chain combined with a sulfated polysaccharide or a glycosaminoglycan, an N-linked sugar chain combined with a sulfated polysaccharide or a glycosaminoglycan, and combinations thereof, wherein the sugar chains are covalently bonded through a peptide to which the sugar chains are added thereby increasing the residual activity of the heparin-binding protein.

20. (Twice Amended) [An improved] A heparin-binding protein comprising a heparin-binding protein containing a peptide sequence to which at least one sugar chain is covalently bonded, wherein the at least one sugar chain is covalently bonded through the peptide sequence to which the at least one sugar chain is added, thereby increasing the residual activity of the heparin-binding protein, said at least one sugar chain selected from the group consisting of a sulfated polysaccharide, a glycosaminoglycan, an O-linked sugar chain combined with a sulfated polysaccharide or a glycosaminoglycan, an N-linked sugar chain combined with a sulfated polysaccharide or a glycosaminoglycan, and combinations thereof.

23. (Amended) [An improved] A heparin-binding protein which comprises a heparin-binding protein modified with covalently bonded sugar chains, the sugar chain being selected from the group consisting of a sulfated polysaccharide, a glycosaminoglycan, an O-linked sugar chain combined with a sulfated polysaccharide or a glycosaminoglycan, an N-linked sugar chain combined with a sulfated polysaccharide or a glycosaminoglycan and combinations thereof, wherein the activity of the heparin-binding protein is greater than the activity of the unmodified protein.